# THE ASSESSMENT OF TOXICITY AFTER EXPOSURE TO A PYROTECHNICALLY-GENERATED AEROSOL

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### **INTRODUCTION**

In the early 70's, the environmental and scientific communities expressed concern regarding the release of chlorofluorocarbons (CFCs) and Halons into the atmosphere. CFCs and Halons are perhalogenated alkanes, that upon reaching the stratosphere, undergo photodegradation from ultraviolet radiation (UVR), releasing chlorine (CFC) or bromine (Halon). These halides react with stratospheric ozone (bromine being 20-60 times more reactive than chlorine) forming a halide monoxide that does not absorb short wavelength UVR (Piver, 1991; Cicerone, 1994; Last, 1993; Lashof and Ahuga, 1990). The result of this interaction is a decrease in the ozone layer and an increase in the amont of short wavelength UVR striking the earths surface. Human health effects associated with exposure to short wavelength UVR include: non-melanoma skin cancers, cataracts and possible adverse effects on immune fbnction (Urbach, 1991; van Kuijk, 1991; Shope, 1991).

Because of these health effects, 26 countries met in Montreal, Canada and agreed to the "Montreal Protocol on Substances that Deplete Ozone Layer" in September of 1987. The Montreal Protocol calls for a 50 percent reduction in CFC and Halon production (current production levels not to exceed those set in 1986). The phase-out of CFCs and Halons was accelerated in June of 1990, when the Montreal Protocol was revised in London, Great Britain per the London Amendment. This revision provided for total production phase-out of CFCs and Halons (Class I ODS) by the year 2000. In November of 1992, the Montreal Protocol was revised again in Copenhagen, Denmark, accelerating production phase-out dates for Halons by the year 1994 and CFCs by the year 1996. These phase-outs have placed pressure upon manufacturers to develop replacements for CFCs and Halons currently used in refrigeration, climate control and fire suppression systems.

In the search for an acceptable alternative to CFCs and Halons, three major areas of fire suppressants have emerged: inert gases, water mist and dry powder aerosol. The use of dry powder aerosols as a fire suppressant is an idea that has been around for several years. These fine aerosols derive their suppression capabilities from chemical and physical mechanisms such as vaporization, decrepidation, decomposition and surface mediated phenomena (Sheinson *et al*, 1993). Spectrex Fire Extinguishant (SFE) is a pyrotechnically-generated dry powder aerosol that is under investigation as a total flooding agent. At a temperature of 500°C or greater, pyrolyzation is initiated producing a finely-dispersed, optically-dense, soluble aerosol. Physical and chemical properties of the aerosol, such as mass concentration, size distribution, specific surface area (SSA), density, morphometry, dynamic behavior and chemical composition have a direct influence upon suppression mechanisms and are important determinants in extinguishment

efficacy (Freidman, 1993; Ewing *et al*, 1989 Ewing *et al*, 1992). These properties are basic determinants of aerosol inhalation toxicity.

The primary question regarding the toxicity of an inhaled aerosol is whether the aerosol will reach the deep lung and dissolve. Particles 1 - 2 mm in diameter will penetrate deep into the tracheobronchial tree, depositing in the alveolar acini where they may possible damage parenchymal tissues and limit clearance/defense mechanisms (Hatch and Gross, 1964). The rate at which deposited particles dissolve in the lung is proportional to the specific surface area (SSA) and the chemical composition of the particle. The predicted by-products of pyrolyzed SFE are alkali aerosol salts of potassium, oxygen and carbon monoxide. At the recommeded manufacturer use concentration, the resulting aerosol of these alkali salts have an estimated median diameter of 1-2 mm. Therefore, knowledge of both chemical and physical aerosol properties are critical in the assessment of both toxicity and extinguishment properties. Potential toxic effects from exposure to SFE aerosol may include: 1) irritation of the lung, resulting in discomfort and/or altered respiration and oxygen uptake; 2) irritation of the skin, nasal area and/or mucous membranes of the eye, resulting in discomfort and/or impaired visual capacity; 3) high aerosol concentration, affecting pulmonary function, resulting in incapacitation and possible death; and 4) the potential presence of carbon monoxide (CO), resulting in increased carboxyhemoglobin levels and decreased oxygen uptake, leading to disorientation and possible incapacitation.

The objective of this study was to examine the physiologically effects of inhaling pyrolyzed SFE. This examination included aerosol characterization (mass concentration, particle size distribution [mass median aerodynamic diameter, MMAD] and particle size analysis [geometric standard deviation, sg]) and toxicity parameters (pulmonary effects).

## MATERIALS AND METHODS

*Chemicals:* SFE Formulations A was supplied by Spectronix Ltd. (Tel Aviv, Israel).

Inhalation Chamber Configuration and Operation: The exposure system consisted of a modified Hinners-type 700 L inhalation chamber with a supply/exhaust system, a specially designed aerosol generator and an exhaust scrubber (Kimmel and Yerkes, 1990). The generator was connected to the inlet side of the system by a 3-inch aluminum duct. The system was operated in the dynamic mode during the pyrolyzation of SFE until the generation of aerosol had ceased and the chamber was filled. Once the chamber was filled rapid activation shut off values in the inlet and exhaust lines were closed to transform the chamber to a static system. The generator consisted of two flanged 4-inch sections of schedule 80 stainless steel pipe bolted together. A 1/8-inch thick sintered stainless steel plate was inserted between the two sections of pipe. Air entered the generator through the lower plenum and passed through the sintered plate into the ignition plenum, The ignitor consisted of a 6 cm 26 gage nichrome wire attached to insulated copper electrodes that were fitted through the wall of the upper plenum. The nichrome wire was coiled to fit in the bottom of a ceramic combustion boat placed on the sintered plate and heated to 550-600°C via a 18 volt/6 amp current to ignite the SFE. A thermocouple was placed 5 cm above the ignitor to monitor the combustion temperatures. Aerosol samples were collected from the center of the chamber and analyzed for concentration, particle size analysis (MMAD) and particle size distribution (sg). The system was exhausted through a scrubber at the conclusion of each exposure.

<u>Aerosol Concentration</u>: The chamber's aerosol mass concentration was determined via filter samples. Samples were collected on a 47 mm Gelman 61631 A/E glass fiber filter placed in a brass filter holder (IN-TOX Products, Albuquerque, **NM**). Filters were stored in a decicator prior to sampling and weighed on a Cahn C-31 Microbalance (Fisher; Cincinnati, OH). Samples were collected at 1, 5 and 15 minutes for 15 minute exposures and 1, 5, 15, 30, 45 and 60 minutes for 60 minute exposures. The flow rate through a filter was 5 L/min with a sampling time of 15 seconds.

Particle Size Distribution and Analysis: Mass weighted particle size distribution was determined using a cascade impactor (IN-TOX Products, Albuquerque, NM). The impactor designs were based on Marple's criteria (Marple, 1978). Aerosol particles were collected on 37 mm stainless steel substrates coated with a layer of apiezon grease/toluene mixture and allowed to dry for 1 hour. A 47 mm Gelman 61631 A/E glass fiber filter was used as a final filter. Substrates and filter were weighed on the Cahn C-31 Microbalance. Samples were collected at the beginning and end of each exposure. The flow rate through the impactors was at 20 L/min with a sampling time of 4 to 15 seconds to maximize sample collection and avoid impactor over load at various mass concentration. Particle size analysis was reported as MMAD and particle size distribution as sg. Aerosol size and number concentration was also analyzed with a TSI model 3300 Aerodynamic Particle Size Analyzer (APS; TSI Corp, St. Paul, MN). The APS obtained the MMAD and particle counts. Two TSI model 3302 diluters each with a 100:1 dilution probe proceeded the **APS** providing a final dilution of 10,000:1. The real time aerosol analysis was performed on a Zenith Data System 286 PC with TSI model 390041 APS Advanced Software, version B using a density value of 2 g/cc. Samples were collected for 10 seconds. The aerosol was sampled at 1, 15, 30, 45 and 60 minutes.

<u>Particle Morphology</u>: Aerosol samples were collected via a cyclone for morphometry, specific surface area (SSA) and density determination. Particle morphometry was determined by computer controlled scanning electron microscope (CCSEM; RJ Lee Group, Inc.). Particle specific surface area (SSA) was determined using Brunauer-Emmitt-Teller (BET) analysis of nitrogen adsorption isotherms. Particle density was determined using pressure pulsed ultrapycnometry. SSA and density determinations were performed on a Quantasorb sorption analyzer (Quantachrome Inc, Syosset, NY)

<u>Animals</u>: Male Fisher CDF (F-344)/Cr1BR rats were obtained from Charles River Breeding Labs (Wilmington, MA). The rats weighed between 200-250 g. Upon arrival, the rats were tail tattooed and quarantined for two weeks. Animals were housed in suspended shoe box type cages. They were provided Formula Lab Chow 5008 (Purina Milles Inc., St. Louis, MO) and reverse osmosis filtered water *ad libitum*.

*Experimental Design:* Animals were randomized first into five exposure groups and then five post-exposure time points. Each exposure group/post-exposure time point consisted of

Group	Nominal Conc. (g/m <sup>3</sup> )	Length of Exposure (min.)	Post-Exposure Observation Time Points					
			1 hour	6 hours	24 hours	7 days	14 days	
1	Control	60	5/5/4	5/5/4	5/5/4	5/5/4	5/5/4	
2	50	15	5/5/4	5/5/4	5/5/4	5/5/4	5/5/4	
3	50	60	5/5/4	5/5/4	5/5/4	5/5/4	5/5/4	
4	80	15	5/5/4	5/5/4	5/5/4	5/5/4	5/5/4	
5	80	60	5/5/4	5/5/4	5/5/4	5/5/4	5/5/4	

fourteen animals; five animals for histopathological examination, five for enzyme analysis, and four for wet/dry lung determination.

<u>*Clinical Observations:*</u> Clinical signs will be recorded during the exposure at 1, 5, 15, 30, 45 and 60 minutes.

<u>Histopathology</u>: Animals were euthanized by an intraperitoneal injection of a Ketamine<sup>TM</sup>/Xylazine<sup>TM</sup> mixture (70 mg/kg Ketamine<sup>TM</sup> [Vetalor; Parke-Davis, Moms Plains, NJ] and 6 mg/kg Xylazine<sup>TM</sup> [Rompun; Mobay Corporation, Shawnee, KS]). and the abdominal and thoracic cavities incised. Gross examination was performed on the trachea, lung, heart and abdominal organs. The trachea and lungs were removed **from** the thoracic cavity and trimmed. The head was removed and cut transversely at the level of the incisive papilla and second palatal ridge using a Buehler Isomet low speed saw with diamond wafering blade (Evanston, E) to examine nasal turbinates. All tissue sections were placed in 10% neutral buffered formalin and decalcified for three days in 10% ethylenediaminetetraacetic acid (EDTA; Sigma, St. Louis, MO). The tissues were processed for histological examination (light microscopy). Each section was embedded in paraffin, sectioned at 3 - 4 microns, and stained with hematoxylin and eosin.

**Enzyme Analysis:** Bronchoalveolar lavage (BAL) was collected and analyzed for protein and selected enzymes. Rats were euthanized with an injection of a Ketamine<sup>TM</sup>/Xylazine<sup>TM</sup> mixture. The thoracic cavity was incised, and the trachea exposed and cannulated. The lungs were infused three times with 3-6 mL of Ca-Mg-free phosphate-buffered saline (PBS), pH 7.2. The BAL from each rat was pooled and centrifuged at 300 x g for 10 min. The cell pellet will be suspended in 5 mL of RPMI 1640 (Gibco, Grand Island, **NY**) containing 25 mM Hepes buffer. The supernate will be analyzed for total protein content, acid phosphatase (ACP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and b-glucuronidase (b-G) activity.

<u>Wet/Dry Luna Weight Determinations:</u> Wet/dry lung ratio was measured by the method described by Staub (1974), with minor modifications. After the animals were euthanized, the thoracic cavity was incised to expose the lung and heart, the cervical trachea was exposed, and the tissue between the thoracic and cervical trachea was excised. The trachea was ligated 1 to 2 mm below the pharynx. After transection of the aorta and vena cava, the heart was excised, the lung was extracted *en bloc*, and the esophagus removed. The lungs were rinsed with saline and blotted dry with gauze pads. A small, preweighed "S" shaped hook was inserted through the

trachea just above the ligature and lung wet weight recorded. The lung was then suspended from a drying rack via the S-hook and placed in a drying oven at  $110^{\circ}$ C for 24 hours. At the conclusion of 24 hours, the lung dry weight was recorded. Corrected lung wet weight (WW) and dry weight (DW) were determined by subtracting the weight of the S-hook. Pulmonary edema formation was quantified by comparison of % water (H<sub>2</sub>O), g of water in the lung/kg of body weight (BW), and g of solid (dehydrated) lung/kg of body weight between the exposed and control groups using the formulas:

% K\_O = (WW-DW)/WW x  $10^2$ g H<sub>2</sub>O/kg BW = (WW-DW)/BW in g x 10' g solids/kg BW = DWBW in g x  $10^3$ 

### **RESULTS**

<u>Inhalation Chamber Operation</u>: A pressure pulse was noted 10-15 seconds after ignition and lasting for 5-10 seconds. Temperatures within the generator ranged from 590 to  $815^{\circ}$ C for a 50 g/m<sup>3</sup> load and 895 to  $1100^{\circ}$ C for a 80 g/m<sup>3</sup> load, regardless of formulation. However, the chamber temperature remained at ambient (22-26°C)

<u>Aerosol Characterization</u>: The actual aerosol chamber concentrations of SFE Formulations A at 50 and 80 g/m<sup>3</sup> are shown in Figure 1. The aerosol concentrations exhibited an exponential decay. The half-life of the aerosol concentration decay was 18.3 minutes for a 50 g/m<sup>3</sup> load and 14.4 minutes for a 80 g/m<sup>3</sup> load (Figure 1). Aerosol size distributions are shown in Table 1. The MMAD and sg ranged from 2.08 to 2.49 mm and from 1.54 to 1.93, respectively, regardless of concentration and formulation. SFE Formulation A aerosols had a tendency to grow in size over time due probably to agglomeration (Figure 2). Electron micrographs of SFE Formulation A cyclone samples showed that the aerosol was a cuboidal crystal and that several crystals were fused together creating particles that were larger than that observed with the impactors (Figure 3). The SSA and density of SFE Formulation A are shown in Table 1.

Table 1: Mean and SEM for Mass Median Aerodynamic Diameter (MMAD;  $\mu$ m) Particle Size Distribution (og), Density (g/cm<sup>3</sup>) and Specific Surface Area (SSA) after the pyrolyzation of SFE Formulation A at a Nominal Load of 50 and 80 g/m<sup>3</sup>.

		1 minute	15 minutes	60 minutes
Nominal Load of 50 g/m <sup>3</sup>	MMAD	$2.0 \pm 0.1$	$2.6 \pm 0.1$	$2.6 \pm 0.1$
	sg	$1.66 \pm 0.10$	$1.58 \pm 0.06$	$1.74 \pm 0.04$
Nominal Load of 80 g/m <sup>3</sup>	MMAD	$2.0 \pm 0.1$	$2.6 \pm 0.1$	$2.6 \pm 0.1$
	sg	$1.66 \pm 0.10$	$1.58 \pm 0.06$	$1.74 \pm 0.04$
Density	2.31	$\pm 0.01$	<u>SSA</u>	$2.74 \pm 0.10$







Figure 3. An electronmicrograph of SFE Formulation A Particles.



Figure 4. Total Protein analysis in BAL of animals exposed to pyrolyzed SFE Formulation A.

<u>Clinical Observations</u>: No deaths were reported during the study. Animals exposed to SFE Formulation **A** exhibited signs of irregular breathing cycles, lack of coordination, lethargy and coughing/sneezing. Head pulling or straining was observed frequently; that is, the animal would extent the head back, up and away **from** the body. As loads and length of exposure increased, these signs became more pronounced. All animals appeared to recover once placed in fresh air. Animals exposed to a nominal concentration of  $80 \text{ g/m}^3$ , irregardless of exposure length, exhibited a yellow viscous material around the nasal area.

**Postmortem:** No lesions were noted on the trachea, lung, heart and abdominal organs after gross examination. However, trace amounts of dried reddish-brown material was found around the nares in 100% of the animals exposed to 80 g SFE/m<sup>3</sup> for 60 minutes (necrospied at 1 hour and 24 hours post-exposure) and 80 g SFE/m<sup>3</sup> for 15 minutes (necrospied at 14 days post-exposure).

<u>Histopathology</u>: Lesions were noted in the nasal turbinates and were limited to those animals exposed to a nominal concentration of 80 g SFE/m<sup>3</sup>. The percentage of animals per post-exposure time points are as follows: 100% at 1 hour, 80% at 6 hours, 100% at 24 hours, 0% at 7 days and 0% at 14 days. Lesions consisted of mild to minimal multifocal necrosuppurative rhinitis, primarily in the respiratory epithelium of the ventro-distial turbinates. There was also some minimal necrosis of olfactory epithelium in the ethmoid turbinates. Edema was noted in the lungs and limited to those animals exposed to a nominal concentration of 80 g SFE/m<sup>3</sup>. The percentage of animals with mild to moderate edema per post-exposure time points are as follows: 40% at 1 hour, 80% at 6 hours, 60% at 24 hours, 0% at 7 days and 0% at 14 days. One animal in the 6-hour post-exposure group had severe edema. In addition to edema moderate to severe pneumonia was present in 40% of the animals at the **24** hour post-exposure time point and in **20%** of the animals at the 7 day post-exposure group. The pneumonia consisted of multifocal to occasionally coaleasing foci of alveoli filled by edema fluid and occasional hemorrhage, with numerous macrophages admixed with lesser lymphocytes, plasma cells, neutrophils and cellular debris.

<u>Wet/Dry Luna Weight Determinations:</u> There was an increase in the % water in the lung and g of water in the lung/kg of body weight for animals exposed to 80 g SFE/m3 for 60 minutes, but was normal for g of solid (dehydrated) lung/kg of body weight when compared against control animals. There was no difference between control and exposure groups for % of water in the lung, g of water in the lung/kg of body weight, and g of solid (dehydrated) lung/kg of body weight.

*Enzyme Analysis:* Total protein was elevated in BAL for animals exposed to 50 and 80 g SFE/m3 for 60 minutes at post-exposure time points of 6 and 24 hours (figure 4). Total protein was normal in all remaining animals. No alterations were noted in acid phosphatase, alkaline phosphatase, lactate dehydrogenase and b-glucuronidase activity of BAL.

#### **DISCUSSION**

The complications associated the with generation of SFE aerosols required modification of the routine procedures normally used to investigate the acute inhalation toxicity of test agents. Steps were taken to dissipate the thermal energy and its corresponding pressure pulse resulting from the ignition of SFE before the test aerosol was transported to the exposure chamber in order to eliminate the influence of these factors in the evaluation of SFE toxicity. Although some transport system losses were noted, the initial aerosol concentrations were comparable with those encountered in other test systems (used for evaluation of fire extinguishment efficacy) in which the SFE, at identical nominal concentration loadings, was ignited within the test chamber volume (data not shown). These studies demonstrated that the transport losses in the toxicity testing exposure system were insignificant, and in some trials, the initial concentration of SFE in the exposure apparatus slightly exceeded that found in the fire extinguishment testing chamber. Thus, there is good agreement with respect to exposure concentration between the toxicity testing trials and tests of SFE fire extinguishment capacity meant to simulate actual deployment conditions. The nominal concentrations (load concentrations ranging between 50 and 80 g/m<sup>3</sup>) have been suggested for deployment in fire extinguishing systems. With single-pulse generation of test material, it was necessary to conduct the exposure using static mode chamber operation. Without continuous replenishment in the exposure system, there was an exponential decay of aerosol concentration over the exposure duration with the different gradients for the higher and lower The exposure profiles and the initial concentration converging at approximately 45 min. convergence of the concentration gradients obhscate the determination of an exposure-response relationship.

Dynamic changes in aerosol size distribution showed a tendency toward an increase in mean diameter over time despite the early initial settling of larger particles. This shift in particle size can be attributed to agglomeration phenomena due to the very high initial particle number concentrations (on the order of  $10^9 - 10^{10}$  particles/cm<sup>3</sup>) and to individual particle hygroscopic growth. Chemical analyses of the aerosol particles showed that they were homogeneous (99+%) alkali salts of potassium. The shift in aerosol size distribution over the exposure duration was not considered significant because at any given time, nearly all of the particles could be considered respirable by PM10 criteria. Likewise, the shift in median diameter might cause a subtle shift in the pulmonary deposition pattern; however, a significant portion of the particles will be preferentially deposited in the distal airways and alveolar spaces.

Clinical observation of cyclic hyper/hypoventilation breathing patterns, choking or head straining responses suggests that SFE aerosol is irritating to mucous membranes. Ignition of SFE has been shown to produce elevated CO and CO, concentrations which significantly increased pCO<sub>2</sub> and carboxyhemaglobin in test animals (subsequent/adjunct studies -- data not reported here). Elevated CO, is likely responsible for the changes in breathing pattern and an overall increase in ventilation which could have led to increased aerosol deposition. The findings of this study indicate that there is a time and dose dependent pulmonary toxicity resulting from exposure to SFE aerosols. The most common insult is the development of interstitial and pulmonary (alveolar) edema which, in most cases resolves, within a week of exposure with very little or no remarkable cellular damage evident. This is confirmed by histological examination of the tissues

and by the elevated protein levels in **BAL** fluids without an accompanying increase in enzyme activities] which would suggest significant tissue and cellular damage and cell death. However, a few of the animals exposed to SFE did develop more severe pulmonary complications resulting in apparent tissue damage particularly in the nasal mucosa. Histological examination demonstrated pulmonary tissue damage in some of the animals as evidenced by cellular debris in alveolar spaces and persistent pneumonitis.

Although the mechanisms of SFE-induced pulmonary edema and tissue damage are not certain, it is feasible that rapid dissolution of the highly soluble SFE particles could lead to some of the observed effects. Particle dissolution could produce a local perturbation of electrolyte balance and regulation in lung tissues, which might disturb hydrostatic homeostasis leading to compartmental shifts of tissue fluids. Hydration expansion of the layer which would decouple the layers and alter mucous (hence particle) transport, may be responsible in part, for the observed accumulation of mucous in the upper airways of exposed animals. Changes in hydrostatic pressure may have resulted in the interstitial edema and, with changes in epithelial permeability the subsequent alveolar edema.

The observed pulmonary changes, though for the most part transient, in nearly all of the animals exposed to the higher concentrations of SFE suggest numerous other possible pulmonary ventilatory and gas exchange effects which merit further investigation. The development of nontransitory tissue damage in the lungs of some of the animals should be investigated further.

## **CONCLUSION**

Exposure to the by-products of pyrolyzed SFE Formulation **A** did not cause acute toxicity in male Fisher rats. However, a reversible edema was noted in those animals exposed to  $80 \text{ g/m}^3$  for 60 minutes. The presence of edema is most likely due to hydrostatic effects and not that of cell death. This is based upon the evidence that only an increase in protein was observed in the BAL fluid with no subsequent increase in enzyme levels. The pyrolyzation of SFE produced aerosol concentrations of  $10^6$ -  $10^8$  particles/cm<sup>3</sup> that agglomerated over time. Even with the agglomeration, the aerosol remained of respirable size. Further investigations of the combustion atmospheres, the formation of edema and ventilation/perfusion capability are needed to define the risk from exposure of SFE Formulation A by-products at load concentrations between  $50 - 80 \text{ g/m}^3$  for exposures up to 60 minutes. Characterization of SFE aerosols generated from the laboratory system and from total flooding systems designed for commercial use are necessary to interpret this toxicological data properly.

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in the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, DHHS, National Institute of Health Publication #85-23, 1985, and the Animal Welfare Act of 1966, as amended.

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